should include UV exposure, even absent specific FDA requirements.

Our resin data (resins P1. P2, P3, P4, P19, and P18) cited by Kelce and Borgert came from at least three replications of stressing, extraction, and EA assays. As described in our "Methods" and "Supplemental Material," the assay variance was very small: SEs were typically smaller than the diameter of the data points of the graphed means. The whole series of 49 assays was repeated only once, but no extract exhibited EA; more recent extracts of the same plastics confirm our original results.

Kelce and Borgert noted that colorants are "embedded" in plastics. However, "bound" colorants in plastic compounds can and do readily leach from plastics. They are additives, which—like most additives—are only rarely chemically bound to polymers. Hence, concerns about all additives are warranted because any can leach from a plastic product.

Regarding broader issues, the objective of our paper was to quantify the prevalence of xenoestrogen release from commonly used plastic products. These data are significant in part to help assess the risk of such products to human health and environmental contamination. Kelce and Borgert cite Charles et al. (2007), who examined some interactions between a small set of phytoestrogens and xenoestrogens. The limited negative results of that study have been contradicted by dozens of other studies (e.g., Patisaul and Jefferson 2010). However, our objective was not to establish definitive links between public health issues, environmental pollution, and exposure to xenoestrogens. This relationship is an active research area, and it will take many years to obtain definitive answers.

Kelce and Borgert's concerns about the paucity of epidemiological data correlating EA exposure via use of plastics with adverse human health effects is analogous to the long-standing controversy for tobacco, which is now highly regulated, largely because increasing numbers of epidemiological studies correlated smoking with heart disease and lung cancer. For decades, it was common to hear tobacco industry spokespersons argue that "[epidemiological] correlation does not mean causation" and demand that molecular, cellular, and/or systemic mechanisms be extensively demonstrated before any action, regulatory or otherwise, be taken. One rarely hears spokespersons for the chemical and plastics industry make this argument for release of chemicals having EA from plastics, because the mechanisms by which tobacco has its effects are still much less well known compared to mechanisms by which chemicals having EA produce adverse health and environmental effects. Instead, we hear, "Where are the epidemiological correlations?" Those correlations are fewer (but not nonexistent) than for tobacco at this relatively young stage of the field, but the number of such publications is rapidly increasing. In the meantime, our study and hundreds to thousands of other *in vitro* studies demonstrate that chemicals having EA have easily measurable effects on all sorts of human cells (including MCF-7 cells). Most scientists in this field believe that such results suggest adverse health effects in humans and that, as such data continue to be gathered, these correlations will become as compelling as did those for the impact of tobacco smoking on public health.

Legislators, consumers, manufacturers, and scientists must judge current industry practices in this area based on available data. Reasonable people can differ. The American Chemistry Council takes the position that until definitive studies consistently show health and environmental hazards from chemicals with EA leaching from plastic products, no industry action need be taken. We disagree. Plastic items are essential consumer products, but we argue that they need to be made safer. Our most recent data show that there is very little extra expense to produce safer plastics that do not leach chemicals having EA; that is, it costs very little at this time to avoid a potential health risk.

C.Z.Y. is employed by, and owns stock in, CertiChem (CCi) and PlastiPure (PPi). S.I.Y. and D.J.K. are employed by PPi. V.C.J. has no financial interests in CCi or PPi, but he was principal investigator for a subcontract at Northwestern Medical School to help develop the MCF-7 assay on NIH grant P30 CA051008 awarded to CCi. G.D.B. owns stock in and is the founder and chief excutive officer of CCi and the founder and chief scientific officer of PPi. All authors had freedom to design, conduct, interpret, and publish research uncompromised by any controlling sponsor.

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References

Charles GD, Gennings C, Tornesi B, Kan HL, Zacharewski TR, Gallapudi BB, et al. 2007. Analysis of the interaction of phytoestrogens and synthetic chemicals: an in vitro/in vivo comparison. Toxicol Appl Pharmacol 218:280–288.

FDA (Food and Drug Administration). 2002, 2007. Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations. Available: http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm081818.htm [accessed 10 August 2011].

Patisaul HB, Jefferson W. 2010. The pros and cons of phytoestrogens. Front Neuroendocinol 31(4):400–419; doi:10.1016/j.yfme.2010.03.003 [Online 27 March 2010].

Wagner M, Oehlmann J. 2010 Endocrine disruptors in bottled mineral water: estrogenic activity in the E-screen. J Steroid Biochem Mol Biol; doi:10.1016/j.jsbrnb.2010.10.007 [Online 2 November 2010].

Yang CZ, Yaniger SI, Jordan VC, Klein DJ, Bittner GD. 2011. Most plastic products release estrogenic chemicals: a potential health problem that can be solved. Environ Health Perspect 119:989–996; doi:10.1289/ehp.1003220 [Online 2 March 2011].

Environmental Factors Develop Different Patterns of Immune Disease

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I read with interest the article by Schmidt (2011) on the sprawling explosion of autoimmune diseases and its link to environmental exposure. Schmidt (2011) summarized the problematic state of the field: Systemic autoimmune diseases are common but thought rare; their clinical identification is far from the medical school description; and they continue to be identified as an autoantibody–target–manifestation scheme. Experience shows that a patient develops different autoantibodies through the lifespan, with different clinical patterns within each phase; deeper investigation shows that organ autoimmune disease is in fact systemic. Likewise, allergy, food intolerance, cancer, and immunodeficiency (all broad diseases that are immune in nature) cross and share autoimmunity. This suggests that immature immune systems are promoted and prevented from natural selection in the era of antibiotics, but they pay the cost of fostered health dysfunctions or diseases exposed to the current complex hostile environment.

I noticed this complex scenario in a survey of 22 patients reporting sick building syndrome (Blasco 2011). Although reported data was limited to autoimmune cases and the involved substances were not yet identified, I found that the same environment triggered and worsened other immune disorders. The health of two patients with asthma inexplicably worsened when they started to work in the building. One patient developed gynecological cancer; another patient, who had a past history of Hodgkin's lymphoma, developed chronic fever and fatigue again that lasted 3 years, until she was relocated. Some of the patients reported new adult onset of clinical intolerance of milk or other foods, and one patient was positive in a breath test for lactose intolerance. A review of family histories revealed that in 20% of the patients, more than one direct relative was affected by cancer. Personnel records showed that allergy

was present in 59% of the patients; recurrent infections during childhood were common; 20% required amigdalectomy. One patient suffered rheumatic fever; one patient had not been effectively immunized after repeated hepatitis vaccines; and another had defective CD4 and suffered recurrent pneumococcal infections.

It would be surprising if these illnesses did not share a common root in the immune system. Schmidt (2011) underlined rising prevalence rates of autoimmunity and discussed causes. I believe that this trend is relevant in general to immune disorders because of different reactions within the same scope of lymphocyte dysfunction in response to our new aggressive environment.

The author declares that he has no actual or potential competing financial interests.

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References

Blasco LM. 2011. Sick building syndrome and autoimmunity. Lupus 20:544–546.

Schmidt CW. 2011. Questions persist: environmental factors in autoimmune disease. Environ Health Perspect 119:A248–A253.

Dietary Intervention and DEHP Reduction

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Rudel et al. (2011) reported a surprising reduction in metabolites of bis(2-ethylhexyl) phthalate (DEHP) in their dietary intervention study, considering that—to the best of the industry's knowledge—the plasticizer is no longer used in the food packaging products that the authors removed from the subjects' dietary routine. Although we question the public health significance of a potential reduction of a few micrograms per liter of DEHP metabolites, we initially saw the study as having the potential to improve our understanding of how low-level exposure to DEHP, suggested by the presence of the metabolites, may be occurring. Unfortunately, in reviewing the Rudel et al. analysis more thoroughly, we were disappointed.

The 56% reduction in mean levels suggested by Rudel et al. (2011) is based on the concentration of DEHP metabolites—before correcting for creatinine levels. With little more than a sentence, Rudel et al. dismissed the accepted practice of correcting for creatinine levels to account for the substantial variability in an individual's urine output. They suggested that such adjustment may "bias associations between urine metabolite concentrations and age or sex" (Rudel et al. 2011) without explaining that the correction is widely used in urinary biomonitoring (by the Centers for Disease Control and most others) to improve the comparability of measurements across individuals.

To their credit, Rudel et al. (2011) did conduct a comparison of the creatinine-adjusted levels of DEHP metabolites and found no statistically significant difference in the mean levels of two of the three metabolites before and after dietary intervention. The authors did not report the change in the adjusted levels of the third metabolite in the article.

The authors also did not address the variability in preintervention levels among the study participants. The presence of two individuals with very high metabolite levels clearly skewed the mean value upward and, consequently, exaggerated the significance of the intervention. Although Table 2 of Rudel et al. (2011) provides the minimum, mean, and maximum values, the variability is best seen in their Supplemental Material, Figure 3 (doi:10.1289/ehp.1003170), and on Silent Spring Institute's web site (Silent Spring Institute 2011). It is unfortunate that Rudel et al. (2011) chose not to address the variability in their article—and a bit surprising—because the postintervention increase in DEHP metabolites was significantly lower than the reported decrease (16% versus 56%).

The author is employed by the American Chemistry Council to represent the manufacturers of phthalates, including DEHP.

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Reference

Rudel RA, Gray JM, Engel CL, Rawsthorne TW, Dodson RE, Ackerman JM, et al. 2011. Food packaging and bisphenol A and bis(2-ethylhexyl) phthalate exposure: findings from a dietary intervention. Environ Health Perspect 119:914–920; doi:10.1289/ehp.1003170 [Online 30 March 2011].

Silent Spring Institute. 2011. Phthalate Levels Decline during 3-Day Fresh Food Diet. Available: http://www.silentspring.org/images/our_research/DEHP_results.jpg [accessed 12 August 2011].

Dietary Intervention and DEHP Reduction: Rudel et al. Respond

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Steven Risotto, representing phthalate manufacturers for the American Chemistry Council (ACC), commented on our study that found a 3-day diet with limited food packaging reduced participants' average bis(2-ethylhexyl) phthalate (DEHP) exposure by > 50% (Rudel et al. 2011).

Risotto's statement that creatinine adjustment by normalization is accepted practice is misleading. Creatinine normalization is appropriate in a longitudinal study if the daily creatinine excretion of the participants remains approximately constant. That assumption is not reasonable in a dietary intervention because short-term changes in diet can strongly influence creatinine levels (Kesteloot and Joossens 1993). In our article (Rudel et al. 2011), we addressed urinary dilution by including creatinine as a variable in the mixed-effects model that estimates exposure reduction from the intervention, as currently recommended by researchers at the Centers for Disease Control and Prevention (Barr et al. 2005). Our analysis showed significant decreases of 53–56% in the three DEHP metabolites. Because creatinine normalization is common, we also included normalized results. Creatinine levels dropped significantly during the intervention, indicating that creatinine normalization artificially reduced the observed change. Nonetheless, results showed a 42–45% decrease in all three DEHP metabolites; the decrease was statistically significant for the most abundant metabolite, MEHHP (mono-(2-ethyl-5-hydroxyhexyl) phthalate).

Risotto also questions whether DEHP reductions are attributable to two individuals with high initial exposures. However, we reported the decreases in geometric means, which are not strongly influenced by a few high values. After removing these two participants, we still observed decreases of 37–42% in the geometric means of DEHP metabolites, and reductions in the two most abundant metabolites remain statistically significant. Removing participants with high preintervention exposures is appropriate if an unknown exposure may have covaried with the intervention, but because the two highest exposures were in different families, such confounding seems unlikely.

As to why DEHP metabolite levels dropped during the intervention but did not increase significantly after the intervention—as discussed in detail in our article (Rudel et al. 2011)—the discrepancy may be attributable to the different-length "washout periods" (~ 48 hr between the beginning of the intervention and the first intervention urine sample, and ~ 36 hr between when participants resumed their regular diet and the first postintervention urine sample).

Risotto questions the public health significance of our observed reduction in DEHP exposure. However, DEHP exposure levels in our study (Rudel et al. 2011)—and in the U.S. population—are similar to or higher than those recently reported to exceed health guidelines. Koch et al. (2011) found that 5 of 108 children studied had daily DEHP intakes in excess of the current U.S. Environmental Protection Agency reference dose, and 25% exceeded the tolerable daily